

L Number	Hits	Search Text	DB	Time stamp
1	8	High ADJ bone ADJ mass	USPAT; US-PGPUB; EPO; JPO; DEFWENT	2003/03/09 19:58
7	2	zmax1 and bone	USPAT; US-PGPUB; EPO; JPO; DEFWENT	2003/03/09 19:58
13	5	(US-5691153-\$).did. or (US-20030026860-\$ or US-20020055139-\$).did. or (WO-200177327-\$ or WO-200192891-\$).did.	USPAT; US-PGPUB; DEFWENT	2003/03/09 20:00
-	2	(US-5691153-\$ or WO-200192891-\$).did.	DEFWENT	2002/06/20 17:02
-	3	(WO-200192891-\$ or US-5691153-\$ or WO-200177327-\$).did.	DEFWENT	2002/06/20 17:06

(FILE 'HOME' ENTERED AT 20:03:59 ON 09 MAR 2003)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICNF' ENTERED
AT 20:04:06 ON 09 MAR 2003

L1 125 S HIGH BONE MASS
L2 4 S L1 AND ZMAX?
L3 4 DUP REM L2 (0 DUPLICATES REMOVED)
L4 4 SORT L3 PY
L5 15 S L1 AND LRP5
L6 8 DUP REM L5 (7 DUPLICATES REMOVED)
L7 8 SORT L6 PY

=> d an ti so au ab 17 8

L7 ANSWER 8 OF 8 MEDLINE
AN 2003079394 IN-PROCESS
TI Six Novel Missense Mutations in the LDL Receptor-Related Protein 5 (
LRP5) Gene in Different Conditions with an Increased Bone Density.
SO AMERICAN JOURNAL OF HUMAN GENETICS, (2003 Mar) 72 (3) 763-71.
Journal code: 0370475. ISSN: 0002-9297.
AU Van Wesenbeeck Liesbeth; Cleiren Erna; Gram Jeppe; Beals Rodney K;
Benichou Olivier; Scopelliti Domenico; Key Lyndon; Renton Tara; Bartels
Cindy; Gong Yaoqin; Warman Matthew L; De Vernejoul Marie-Christine;
Bollerslev Jens; Van Hul Wim
AB Bone is a dynamic tissue that is subject to the balanced processes of bone
formation and bone resorption. Imbalance can give rise to skeletal
pathologies with increased bone density. In recent years, several genes
underlying such sclerosing bone disorders have been identified. The LDL
receptor-related protein 5 (**LRP5**) gene has been shown to be
involved in both osteoporosis-pseudoglioma syndrome and the **high**
-bone-mass phenotype and turned out to be an important
regulator of peak bone mass in vertebrates. We performed mutation analysis
of the **LRP5** gene in 10 families or isolated patients with
different conditions with an increased bone density, including endosteal
hyperostosis, Van Buchem disease, autosomal dominant osteosclerosis, and
osteopetrosis type I. Direct sequencing of the **LRP5** gene
revealed 19 sequence variants. Thirteen of these were confirmed as
polymorphisms, but six novel missense mutations (D111Y, G171R, A214T,
A214V, A242T, and T253I) are most likely disease causing. Like the
previously reported mutation (G171V) that causes the **high-**
bone-mass phenotype, all mutations are located in the
aminoterminal part of the gene, before the first epidermal growth
factor-like domain. These results indicate that, despite the different
diagnoses that can be made, conditions with an increased bone density
affecting mainly the cortices of the long bones and the skull are often
caused by mutations in the **LRP5** gene. Functional analysis of the
effects of the various mutations will be of interest, to evaluate whether
all the mutations give rise to the same pathogenic mechanism.

(FILE 'HOME' ENTERED AT 20:03:59 ON 09 MAR 2003)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED
AT 20:04:06 ON 09 MAR 2003

L1 125 S HIGH BONE MASS
L2 4 S L1 AND ZMAX?
L3 4 DUP REM L2 (0 DUPLICATES REMOVED)
L4 4 SORT L3 PY

=> d an ti so au ab pi l4 1-14

L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS
AN 2001:886643 CAPLUS
DN 136:32816
TI Regulating lipid levels via the human **Zmax1** or **high-**
bone-mass HBM gene
SO PCT Int. Appl., 409 pp.
CODEN: PIXXD2
IN Carulli, John P.; Little, Randall D.; Recker, Robert R.; Johnson, Mark L.
AB The present invention relates to the **high bone**
mass (HBM) gene, the corresponding wild-type gene (**Zmax1**
) , and mutants thereof. The **Zmax1**/HBM gene was located on
chromosome 11q13.3 by genetic linkage and mutation anal. Cloning methods
using bacterial artificial chromosomes enabled focus on the chromosome
region of 11q13.3 and sequencing of the autosomal dominant gene. A
guanine-to-thymine polymorphism at position 582 (glycine-to-valine at
position 171 in the protein) in **Zmax1** gene produces the HBM gene
and the HBM phenotype as well as altered lipid levels. Hybridization for
Zmax1 is primarily detected in areas of bone involved in
remodeling, including the endosteum and trabecular bone within the
metaphysis; pos. signals are also obsd in selected bone lining cells of
the periosteum and epiphysis and in chondrocytes within the growth plate.
The genes identified in the present invention are implicated in regulation
of physiol. lipid levels, and thereby lipid-mediated diseases and
conditions. The invention also provides nucleic acids, including coding
sequences, oligonucleotide primers and probes, proteins, cloning vectors,
expression vectors, transformed hosts, methods of developing
pharmaceutical compns., methods of identifying mols. involved in lipid
level regulation in a subject. In preferred embodiments, the present
invention is directed to methods for treating and preventing
atherosclerosis, arteriosclerosis cardiovascular disease, atherosclerotic
and arteriosclerotic assocd. conditions.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 2001092891	A2	20011206	WO 2001-US16946	20010525
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1285002	A2	20030226	EP 2001-948240	20010525
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			

L4 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS
AN 2001:763189 CAPLUS
DN 135:328141
TI Human gene **Zmax1** of 11q13.3, HBM (**high bone**
mass) allele, encoded polypeptides, and their diagnostic and
therapeutic uses
SO PCT Int. Appl., 443 pp.
CODEN: PIXXD2
IN Carulli, John P.; Little, Randall D.; Recker, Robert R.; Johnson, Mark L.
AB The present invention relates to methods and materials used to isolate and
detect a **high bone mass** gene and a

corresponding wild-type gene, and mutants thereof. The present invention also relates to the **high bone mass** allele, the corresponding wild-type gene, **Zmax1**, and mutants thereof. The genes identified in the present invention are implicated in bone development and in focal adhesion signaling. The invention also provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compns., methods of identifying mols. involved in bone development, and methods of diagnosing and treating diseases involved in bone development. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis. The invention describes expanded pedigree anal. and genetic linkage anal. of a **high bone mass** (HBM) gene now known as an allele of human gene **Zmax1**. Older individuals with the HBM allele do not show loss of bone mass compared to normal individuals, do not have osteoporosis, and do not have any known **high bone mass** syndrome. Gene **Zmax1** was localized between genetic markers on human chromosome 11q13.3 and subsequently, BAC clones with the gene were sequenced. The HBM allele is inherited as an autosomal dominant gene and is a G to A mutation at nucleotide 582 in exon 3 which results in a G171V substitution in the encoded protein. Addnl. genotyping of 911 individuals established that the HBM allele is rare and never found in unaffected individuals. "Silent" SNPs (single nucleotide polymorphisms) in the gene **Zmax1** region were also identified. Gene **Zmax1** encodes an LDL-receptor-related protein and the HBM mutation occurs in a conserved region of the presumed extracellular domain. Proteins interacting with the cytoplasmic domain of gene **Zmax1** protein in a yeast two-hybrid assay were identified and include many proteins found at cell-cell and cell-matrix contact sites. These results suggest a potential role for gene **Zmax1** in focal adhesion signaling and suggest that regulating gene **Zmax1** expression or protein binding may affect bone processes.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001077327	A1	20011018	WO 2000-US16951	20000621
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DJ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	EP 1268775	A1	20030102	EP 2000-941578	20000621
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS
AN 2002:888494 CAPLUS
DN 137:381503
TI Compositions and methods for modulating Dkk-mediated protein interactions and their diagnostic and therapeutic uses
SO PCT Int. Appl., 376 pp.
CODEN: PIXXD2
IN Allen, Kristina; Anisowicz, Anthony; Bhat, Bheem M.; Damagnez, Veronique; Robinson, John Allen; Yaworsky, Paul J.
AB The present invention provides reagents, compds., compns., and methods relating to interactions of the extracellular domain of LRP5/**ZMax1**, HBM (a variant of LRP5), and/or LRP6 with Dkk, including Dkk-1. The various nucleic acids, polypeptides, antibodies, assay methods, diagnostic methods, and methods of treatment of the present invention are related to and impact on Dkk, LRP5, LRP6, HBM, and Wnt signaling. The invention claims sequences for peptide aptamers which bind to LRP5 or Dkk-1 and sequences for Dkk-1 peptides which are recognized by antibodies. HBM is a Gly171Val polymorphism in LDL receptor-related protein LRP5/**Zmax**, which has been identified as conferring a **high bone mass** phenotype in a population of related humans. The protein dickkopf-1 (Dkk-1) is required for head formation in early development and

murine limb morphogenesis and is reported to be an antagonist of the Wnt signaling pathway. Dkk-1 protein interacts with the ligand-binding domain of LRP5. Dkk-1 also binds to LRP6, but the EGF repeat domains of LRP6 rather than the ligand-binding domain are required for interaction. Dkk-1 is able to repress LRP5-mediated Wnt signaling but not HBM-mediated Wnt signaling and Dkk-1 also inhibits LRP6 activity. LRP5, LRP6, HBM, Dkk and Wnt are implicated in bone and lipid cellular signaling. Thus, the present invention provides reagents and methods for modulating lipid levels and/or bone mass and is useful in the treatment and diagnosis of abnormal lipid levels and bone mass disorders, such as osteoporosis. Examples of the invention include a yeast two-hybrid screen for Dkk-1 interacting proteins, generation of LRP5 polymorphism-specific antibodies and Dkk-1 specific antibodies, effects of exogenous Dkk-1 on Wnt-mediated signaling in the Xenopus embryo assay, and effects of recombinant Dkk and Wnt3a/1 on TCF-luciferase reporter gene expression in human cell lines with endogenous LRP5/6.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2002092015	A2	20021111	WO 2002-US15982	20020517
	W: AE, AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, ME, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, ME, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS

AN 2002:888430 CAPLUS

DN 137:380994

TI High bone mass variants of the human Zmax1/LRP5 gene modulate bone mass and lipid levels

SO PCT Int. Appl., 629 pp.

CODEN: PIXXD2

IN Allen, Kristina; Anisowicz, Anthony; Graham, James R.; Morales, Arturo; Yaworsky, Paul J.; Liu, Wei

AB The present invention relates to methods and materials used to express an HBM-like polypeptide derived from HBM (high bone mass), LRP5 or LRP6 in animal cells and transgenic animals. The HBM gene comprises 23 exons on human chromosome 11q13.3, and is shown to be an allele of the Zmax1/LRP5 gene; a variety addnl. single nucleotide polymorphisms are also identified. The Zmax1 (LRP5) protein with a glycine-170-valine substitution causes a HMB phenotype involving high bone mass and modified lipid levels, whereas the valine-170 isoform does not. This mutation is in the propeller 1 domain of the protein, and modulates Wnt signaling, Dkk activity, and/or LRP5/6 activity. The present invention also relates to transgenic animals expressing the HBM-like polypeptides. The invention provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compns., methods of identifying mols. involved in bone development, and methods of diagnosing and treating diseases involved in bone development and lipid modulation. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	WO 2002092000	A2	20021121	WO 2002-US14877	20020513
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, ME, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

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L7 ANSWER 1 OF 8 MEDLINE
 AN 2002311732 MEDLINE
 TI Localization of the gene causing autosomal dominant osteopetrosis type I to chromosome 11q12-13.
 SO JOURNAL OF BONE AND MINERAL RESEARCH, (2002 Jun) 17 (6) 1111-7.
 Journal code: 8610640. ISSN: 0884-0431.
 AU Van Hul Els; Gram Jeppe; Bollerslev Jens; Van Wesenbeeck Liesbeth; Mathysen Danny; Andersen Poul Erik; Vanhoenacker Filip; Van Hul Wim
 AB The osteopetroses are a heterogeneous group of genetic conditions characterized by increased bone density due to impaired bone resorption by osteoclasts. Within the autosomal dominant form of osteopetrosis, the radiological type I (ADOI) is characterized by a generalized osteosclerosis, most pronounced at the cranial vault. The patients are often asymptomatic but some suffer from pain and hearing loss. ADOI is the only type of osteopetrosis not associated with an increased fracture rate. Linkage analysis in two families with ADOI from Danish origin enabled us to assign the disease-causing gene to chromosome 11q12-13. A summated maximum lod score of +6.54 was obtained with marker D11S1889 and key recombinants allowed delineation of a candidate region of 6.6 cM between markers D11S1765 and D11S4113. Previously, genes causing other conditions with abnormal bone density have been identified from this chromosomal region. The TCIRG1 gene was shown to underly autosomal recessive osteopetrosis (ARO), and, recently, mutations in the **LRP5** gene were found both in the osteoporosis-pseudoglioma syndrome and the **high bone mass** trait. Because both genes map within the candidate region for ADOI, it can not be excluded that ADOI is caused by mutations in either the TCIRG1 or the **LRP5** gene.

L7 ANSWER 2 OF 8 MEDLINE
 AN 2002274995 MEDLINE
 TI High bone density due to a mutation in LDL-receptor-related protein 5.
 SO NEW ENGLAND JOURNAL OF MEDICINE, (2002 May 16) 346 (20) 1513-21.
 Journal code: 0255562. ISSN: 1533-4406.
 AU Boyden Lynn M; Mao Junhao; Belsky Joseph; Mitzner Lyle; Farhi Anita; Mitnick Mary A; Wu Dianqing; Insogna Karl; Lifton Richard P
 AB BACKGROUND: Osteoporosis is a major public health problem of largely unknown cause. Loss-of-function mutations in the gene for low-density lipoprotein receptor-related protein 5 (**LRP5**), which acts in the Wnt signaling pathway, have been shown to cause osteoporosis-pseudoglioma. METHODS: We performed genetic and biochemical analyses of a kindred with an autosomal dominant syndrome characterized by high bone density, a wide and deep mandible, and torus palatinus. RESULTS: Genetic analysis revealed linkage of the syndrome to chromosome 11q12-13 (odds of linkage, >1 million to 1), an interval that contains **LRP5**. Affected members of the kindred had a mutation in this gene, with valine substituted for glycine at codon 171 (**LRP5V171**). This mutation segregated with the trait in the family and was absent in control subjects. The normal glycine lies in a so-called propeller motif that is highly conserved from fruit flies to humans. Markers of bone resorption were normal in the affected subjects, whereas markers of bone formation such as osteocalcin were markedly elevated. Levels of fibronectin, a known target of signaling by Wnt, a developmental protein, were also elevated. In vitro studies showed that the normal inhibition of Wnt signaling by another protein, Dickkopf-1 (**Dkk-1**), was defective in the presence of **LRP5V171** and that this resulted in increased signaling due to unopposed Wnt activity. CONCLUSIONS: The **LRP5V171** mutation causes high bone density, with a thickened mandible and torus palatinus, by impairing the action of a normal antagonist of the Wnt pathway and thus increasing Wnt signaling. These findings demonstrate the role of altered **LRP5** function in **high bone mass** and point to **Dkk** as a potential target for the prevention or treatment of osteoporosis.

L7 ANSWER 3 OF 8 MEDLINE
 AN 2001694099 MEDLINE
 TI A mutation in the LDL receptor-related protein 5 gene results in the autosomal dominant **high-bone-mass** trait.
 SO AMERICAN JOURNAL OF HUMAN GENETICS, (2002 Jan) 70 (1) 11-9.
 Journal code: 0370475. ISSN: 0002-9297.
 AU Little Randall D; Carulli John P; Del Mastro Richard G; Dupuis Josee;

Osborne Mark; Folz Colleen; Manning Susan P; Swain Pamela M; Zhao Shan-Chuan; Eustace Brenda; Lappe Michelle M; Spitzer Lia; Zweier Susan; Braunschweiger Karen; Benchekroun Youssef; Hu Xintong; Adair Ronald; Chee Linda; FitzGerald Michael G; Tulig Craig; Caruso Anthony; Tzellas Nia; Bawa Alicia; Franklin Barbara; McGuire Shannon; Nogues Xavier; Gong Gordon; Allen Kristina M; Anisowicz Anthony; Morales Arturo J; Lomedico Peter T; Recker Susan M; Van Eerdewegh Paul; Recker Robert R; Johnson Mark L

AB Osteoporosis is a complex disease that affects >10 million people in the United States and results in 1.5 million fractures annually. In addition, the high prevalence of osteopenia (low bone mass) in the general population places a large number of people at risk for developing the disease. In an effort to identify genetic factors influencing bone density, we characterized a family that includes individuals who possess exceptionally dense bones but are otherwise phenotypically normal. This **high-bone-mass** trait (HBM) was originally localized by linkage analysis to chromosome 11q12-13. We refined the interval by extending the pedigree and genotyping additional markers. A systematic search for mutations that segregated with the HBM phenotype uncovered an amino acid change, in a predicted beta-propeller module of the low-density lipoprotein receptor-related protein 5 (**LRP5**), that results in the HBM phenotype. During analysis of >1,000 individuals, this mutation was observed only in affected individuals from the HBM kindred. By use of in situ hybridization to rat tibia, expression of **LRP5** was detected in areas of bone involved in remodeling. Our findings suggest that the HBM mutation confers a unique osteogenic activity in bone remodeling, and this understanding may facilitate the development of novel therapies for the treatment of osteoporosis.

L7 ANSWER 4 OF 8 SCISEARCH COPYRIGHT 2003 ISI (R)

AN 2002:811045 SCISEARCH

TI The gene for **high bone mass**

SO ENDOCRINOLOGIST, (SEP-OCT 2002) Vol. 12, No. 5, pp. 445-453.

Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.

ISSN: 1051-2144.

AU Johnson M L (Reprint); Picconi J L; Recker R R

AB The mass, density, and architecture of the skeleton are adapted to enable it to perform its mechanical, protective, and metabolic functions. Osteoporosis is a condition of lost adaptation characterized by decreased skeletal mass and density and increased skeletal fragility. Many diseases result in increased bone density, including osteopetrosis and Paget's disease, but deformities or bony lesions with decreased skeletal integrity usually accompany these conditions. We have identified a kindred with **high bone mass** (HBM) yet normally shaped bones. Linkage analysis localized the gene for the HBM trait to chromosome 11 (11q12-13). Subsequent physical mapping and mutation analysis have identified the cause as a point mutation in the LDL receptor-related protein 5 (**Lrp5**) gene that results in a valine substitution for glycine at position 171 in the protein. This protein is important in the Wnt signaling pathway. The authors have hypothesized that the **Lrp5** gene/pathway is part of the mechanism by which bone senses mechanical load. Increased bone strength, HBM, and a phenotype resembling our human kindred develop in trans, genic mice carrying the human **Lrp5** gene with the HBM mutation. Recent data indicate that the HBM mutation reduces the threshold for response of the skeleton to mechanical load resulting in an overadaptation to normal mechanical loads. This discovery has opened the door to understanding one of the most important paradigms in bone biology, how bones respond and adapt to mechanical loading. Understanding the mechanosensation pathway and its regulation will lead us to new treatments for osteoporosis.

L7 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS

AN 2002:888886 CAPLUS

DN 138:3282

TI Alleles of the LRP5 gene affecting bone mass and their use in a transgenic animal model of bone mass modulation

SO PCT Int. Appl., 603 pp.

CODEN: PIXXD2

IN Babij, Philip; Bex, Frederick James, III; Yaworsky, Paul J.; Bodine, Peter

Van Nest

AB Transgenic cells and animals expressing foreign genes affecting bone mass are described for use in the study of disease affecting bone mass such as osteoporosis. An allele of the human LRP5 gene (the HBM allele) that has an elevated bone mass phenotype are described. The present invention also relates to transgenic animals expressing the high bone mass gene, the corresponding wild-type gene, and mutants thereof. The invention provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compns., methods of identifying mols. involved in bone development, and methods of diagnosing and treating diseases involved in bone development. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis. Transgenic mice expressing the HBM allele of the human LRP5 gene showed significantly increased bone d. than did control animals.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092764	A2	20021121	WO 2002-US14876	20020513

PI W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L7 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2003 ACS

AN 2002:888494 CAPLUS

DN 137:381503

TI Compositions and methods for modulating Dkk-mediated protein interactions and their diagnostic and therapeutic uses

SO PCT Int. Appl., 376 pp.

CODEN: PIXXD2

IN Allen, Kristina; Anisowicz, Anthony; Bhat, Bheem M.; Damagnez, Veronique; Robinson, John Allen; Yaworsky, Paul J.

AB The present invention provides reagents, compds., compns., and methods relating to interactions of the extracellular domain of **LRP5** /ZMax1, HBM (a variant of **LRP5**), and/or LRP6 with Dkk, including Dkk-1. The various nucleic acids, polypeptides, antibodies, assay methods, diagnostic methods, and methods of treatment of the present invention are related to and impact on Dkk, **LRP5**, LRP6, HBM, and Wnt signaling. The invention claims sequences for peptide aptamers which bind to **LRP5** or Dkk-1 and sequences for Dkk-1 peptides which are recognized by antibodies. HBM is a Gly171Val polymorphism in LDL receptor-related protein **LRP5**/Zmax, which has been identified as conferring a **high bone mass** phenotype in a population of related humans. The protein dickkopf-1 (Dkk-1) is required for head formation in early development and murine limb morphogenesis and is reported to be an antagonist of the Wnt signaling pathway. Dkk-1 protein interacts with the ligand-binding domain of **LRP5**. Dkk-1 also binds to LRP6, but the EGF repeat domains of LRP6 rather than the ligand-binding domain are required for interaction. Dkk-1 is able to repress **LRP5**-mediated Wnt signaling but not HBM-mediated Wnt signaling and Dkk-1 also inhibits LRP6 activity. **LRP5**, LRP6, HBM, Dkk and Wnt are implicated in bone and lipid cellular signaling. Thus, the present invention provides reagents and methods for modulating lipid levels and/or bone mass and is useful in the treatment and diagnosis of abnormal lipid levels and bone mass disorders, such as osteoporosis. Examples of the invention include a yeast two-hybrid screen for Dkk-1 interacting proteins, generation of **LRP5** polymorphism-specific antibodies and Dkk-1 specific antibodies, effects of exogenous Dkk-1 on Wnt-mediated signaling in the Xenopus embryo assay, and effects of recombinant Dkk and Wnt3a/1 on TCF-luciferase reporter gene expression in human cell lines with endogenous **LRP5**/6.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 2002092015 A2 20021121 WO 2002-US15982 20020517
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L7 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS

AN 2002:888480 CAPLUS

DN 137:380994

TI High bone mass variants of the human Zmax1/LRP5 gene modulate bone mass and lipid levels

SO PCT Int. Appl., 629 pp.

CODEN: PIXXD2

IN Allen, Kristina; Anisowicz, Anthony; Graham, James R.; Morales, Arturo; Yaworsky, Paul J.; Liu, Wei

AB The present invention relates to methods and materials used to express an HBM-like polypeptide derived from HBM (high bone mass), LRP5 or LRP6 in animal cells and transgenic animals. The HBM gene comprises 23 exons on human chromosome 11q13.3, and is shown to be an allele of the Zmax1/LRP5 gene; a variety addnl. single nucleotide polymorphisms are also identified. The Zmax1 (LRP5) protein with a glycine-170-valine substitution causes a HMB phenotype involving high bone mass and modified lipid levels, whereas the valine-170 isoform does not. This mutation is in the propeller 1 domain of the protein, and modulates Wnt signaling, Dkk activity, and/or LRP5/6 activity. The present invention also relates to transgenic animals expressing the HBM-like polypeptides. The invention provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compns., methods of identifying mols. involved in bone development, and methods of diagnosing and treating diseases involved in bone development and lipid modulation. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis.

PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 2002092000 A2 20021121 WO 2002-US14877 20020513
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L7 ANSWER 8 OF 8 MEDLINE

AN 2003079394 IN-PROCESS

TI Six Novel Missense Mutations in the LDL Receptor-Related Protein 5 (LRP5) Gene in Different Conditions with an Increased Bone Density.

SO AMERICAN JOURNAL OF HUMAN GENETICS, (2003 Mar) 72 (3) 763-71.
Journal code: 0370475. ISSN: 0002-9297.

AU Van Wesenbeeck Liesbeth; Cleiren Erna; Gram Jeppe; Beals Rodney K; Benichou Olivier; Scopelliti Domenico; Key Lyndon; Renton Tara; Bartels Cindy; Gong Yaoqin; Warman Matthew L; De Vernejoul Marie-Christine; Bollerslev Jens; Van Hul Wim

AB Bone is a dynamic tissue that is subject to the balanced processes of bone formation and bone resorption. Imbalance can give rise to skeletal pathologies with increased bone density. In recent years, several genes underlying such sclerosing bone disorders have been identified. The LDL receptor-related protein 5 (LRP5) gene has been shown to be involved in both osteoporosis-pseudoglioma syndrome and the high-bone-mass phenotype and turned out to be an important

regulator of peak bone mass in vertebrates. We performed mutation analysis of the **LRP5** gene in 10 families or isolated patients with different conditions with an increased bone density, including endosteal hyperostosis, Van Buchem disease, autosomal dominant osteosclerosis, and osteopetrosis type I. Direct sequencing of the **LRP5** gene revealed 19 sequence variants. Thirteen of these were confirmed as polymorphisms, but six novel missense mutations (D111Y, G171R, A214T, A214V, A242T, and T253I) are most likely disease causing. Like the previously reported mutation (G171V) that causes the **high-bone-mass** phenotype, all mutations are located in the aminoterminal part of the gene, before the first epidermal growth factor-like domain. These results indicate that, despite the different diagnoses that can be made, conditions with an increased bone density affecting mainly the cortices of the long bones and the skull are often caused by mutations in the **LRP5** gene. Functional analysis of the effects of the various mutations will be of interest, to evaluate whether all the mutations give rise to the same pathogenic mechanism.

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